REMARKS

Claims 1, 14, and 29 have been amended. The amendments to claims 1 and 29 are supported at least by paragraphs 0028, 0046, and 0048, Example 5 and Table 6 of the specification as filed. Support for the amendment to claim 14 is found in at least paragraph 0019. Claims 3-4, 12, 15, 21-28 and 30-34 have been cancelled hereby. New claims 35-47 have been added. Support for the new claims is found at least at paragraphs 0088, Figure 2, Example 5 and Table 6 of the specification as filed.

Claims 1, 5, 13-14, 29 and 35-47 are presently pending in the case.

Reconsideration of the present case in view of the above amendments and the remarks herein is requested.

Claim rejections under 35 USC 112

Claims 21-34 were rejected under 35 U.S.C. §112 (second paragraph) as allegedly indefinite in the use of the term "FPF_{4+F}". This rejection is respectfully traversed as to the pending claims.

The test of definiteness is whether one of ordinary skill in the art would understand what is claimed in the patent. *Bausch and Lomb, Inc. v Alcorn Laboratories*, 53 USPQ2d 1353 (WDNY 1999). The specification is quite clear as to the meaning of "FPF_{4+F}":

> [0025] As used herein, "FPF_{4+F}" refers to the fraction of fine particles depositing on stage 4 and the filter in the MSLI, independent of flow rate. This is analogous to a patient inhaling at different inspiratory rates into a constant lung architecture. The particle stopping distance and hence the deposition profile will change depending on inhalation flow rate Q. Hence FPF_{4+F}, provides a measure of the flow rate dependence of a test aerosol formulation.

Specification, paragraph 0025.

As further shown in Figure 2, "4 + F" simply means the total of particles trapped by stage four plus the filter of the MSLI (Multi Stage Liquid Impactor). These are thus the smallest particle stages, thus define those particles sized to reach the intended target of the deep lung. These are well known to, and disclosed in, the art.

Claim rejections under 35 USC 103(a)

Claims 1, 3-5, 11-15 and 21-34 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent No. 5,934,273 to Andersson et al, in view of PCT Publication WO 96/32096 to Eljamal et al, U.S. Patent No. 5,855,913 to Hanes et al and U.S. Patent No. 5,049,389 to Radhakrishnan, as evidenced by Swarbrick et al. The rejection is traversed as to amended claims 1, 5, 13-14 and 29.

Andersson et al, Eljamal et al, Hanes et al, Radhakrishnan, and Swarbrick et al do not render independent claim 1, for example, unpatentable. Claim 1 is to a method for the pulmonary administration of a dry powder composition comprising, *inter alia*, particles comprising a hollow and porous lipid matrix and an active agent, and the particles having a particle size of 0.5 to 20 microns, mass median aerodynamic diameter of less than about 5 microns, and the powder comprising a bulk density of less than 0.5 g/cm^3; and loading the dry powder composition into a passive dry powder inhaler and administering the dry powder composition from the inhaler to the respiratory tract of a patient, wherein the lung deposition is greater than 25% for flow rates from 10 to 60 liters per minute. Andersson et al discloses neither the method, nor the powder composition as set forth in claim 1.

Andersson does NOT teach a lung deposition of particles to the deep lung of more than 25% as claimed. There is no direct measure of particle delivery to the deep lung, as taught and claimed by Applicants, and as measured by the FPF_{4+F}. Anderrson does not teach, suggest or disclose a FPF measurement. The composition taught by Andersson is relevant to Andersson's FPF omission. Andersson does not teach a composition that contains the same powder components as taught by Applicants. Thus Andersson does not teach, for example, a

phospholipid matrix, or a hollow or porous particle. The disclosure of Andersson is devoid of any teaching of any lipid, especially a phospholipid, as claimed by Applicants. One need only compare the statements of the respective inventions to illustrate the difference between the two compositions. Andersson defines the problem to be solved as:

> It is known that optimal deposition of powder particles in the lung occurs when the particle diameter is under 10 microns, since particles having a diameter above this range are preferentially deposited in the mouth and throat. However, **such fine powder will typically tend either to cling to the sides of its container, or to clump, so that a high proportion of the powder takes the form of large, loosely structured agglomerates of a size much larger than 10 microns**, and only a small percentage of the powder particles remain within the primary particle diameter range....*[emphasis added]*

Andersson Column 2, lines 8-16.

and the resolution as:

> In order to dispense the pharmaceutically active compound in the form of particles of the necessary diameter, the powder contained in the inhaler is preferentially made up of primary particles or agglomerates of primary particles, which **primary particles preferably are micronized particles** at least 80% (and more preferably at least 90%) of which have a particle diameter of less than about 10 microns. More preferably, at least 50% (and even more preferably at least 60%) of the primary particles have a diameter of less than about 5 microns. *[emphasis added]*
>
> **By processing the primary particles into sturdy agglomerates containing multiple primary particles each**, the physical properties of the powder during storage, handling, and measuring are improved, and less powder is lost on the sidewalls of the device. The agglomerates remain friable, however, so that just prior to entering the respiratory track of the patient, they are readily pulverized into much smaller agglomerates and/or discrete primary particles of a diameter appropriate for deposition in the lung (i.e., less than 10 microns, and preferably less than 5 microns). **In some types of DPI's (e.g., TURBUHLAER and MONOHALER), this deagglomeration is accomplished by a design which creates air turbulence within the device from the air flow generated by inhalation through the device**. *[emphasis added]*

Andersson Column 3, lines 23-47.

Micronized particles are not, *a priori*, hollow or porous particles. Simply put, Andersson teaches a formulation comprising agglomerates of solid particles as beneficial to storage, handling and measuring, then **relies upon a specially-designed inhaled device to break them** up into what is hoped are sufficiently small to reach the intended target area, i.e., the deep lung, to permit systemic absorption.

By contrast, Applicants teach and claim a method for lung delivery wherein the composition is expressly made to be light (low density) hollow and porous, having a phospholipid structural matrix. Such particles are described thus by Applicants:

> [0013] In contrast to the prior art emphasis on device design to address issues commonly associated with patient variability in inspiratory effort, the present invention is directed to a particle engineering approach to overcome such issues. **It has surprisingly been found that the particles of the present invention when administered from a simple passive DPI result in an emitted dose and lung deposition that is substantially independent of device resistance and inspiratory effort, respectively.** Additionally, it has been discovered that particles of the present invention achieve an unexpectedly more rapid absorption of agent when administered via inhalation. *[emphasis added]*
>
> [0014] The present invention provides for dry powder compositions of phospholipid suitable for drug delivery. **According to a preferred embodiment, the phospholipid compositions are efficiently delivered to the deep lung.** The phospholipid may be delivered alone, as in the case of lung surfactant or in combination with another active agent and/or excipient. According to one embodiment, the compositions of the present invention may be delivered from a simple passive DPI device. **The present compositions allow for more efficient delivery to the lung.** *[emphasis added]*
>
> [0015] It is a further aspect of the present invention that the improvements in dispersibility obtained by the present compositions allow for a simple, passive inhaler device to be utilized, in spite of the fact that particles less than 5 [microns] are contemplated and generally preferred. Present state-of-the-art formulations for fine particles utilize blends with large lactose particles to improve dispersibility. When placed in a passive DPI device such formulations exhibit a

> strong dependence of emitted dose and lung deposition on the patient's inspiratory flowrate. **The present compositions exhibit little flowrate dependence on the emitted dose and lung deposition.** *[emphasis added]*

Specification, paragraphs 0013-0015.

Thus the present invention contemplates particles engineered to be light and porous, and are thus suitable for use with a variety of passive inhalers while affording the beneficial property of providing high lung doses while being substantially independent of device (user) flow rate.

The other references do not make up for the deficiencies of Andersson et al. Moreover, there is no basis in either reference for combining it with any of the others. Eljamal et al is orthogonal to both Andersson and the Applicants' claimed invention in that it represents yet another approach to pulmonary delivery of dry powder medicaments. Thus Eljamal et al utilizes a water-soluble polypeptide to improve dispersibility, hence emitted dose of a dry powder. In addition, Eljamal et al teaches the use of an active inhaler which requires a high velocity gas stream to entrain and aerosolize the powder. This is inapposite to Applicants' specifically engineered powder designed and intended for use with a **passive** dry powder inhaler, and by which the desired dosage is provided over a range of patient flow rates. Similarly, Hanes et al, Radhakrishnan, and Swarbrick et al do not teach, at least the use of a passive dry powder inhaler. As such, they are not relied on to make up for this deficiency in Andersson et al, nor do they. Accordingly, no reference or combination of references arrives at an administration as recited in claim 1. Accordingly, the Examiner has not established a prima facie case under 35 U.S.C. §103(a).

For at least these reasons, amended independent claim 1 and claims dependent therefrom, are not properly rejectable under 35 U.S.C. §103(a) as being unpatentable over Andersson et al, Eljamal et al, Hanes et al, Radhakrishnan and Swarbrick et al. Applicants thus request withdrawal of the rejection of claims 1, 5 and 13-14 under 35 U.S.C. §103(a).

Moreover, amended independent claim 29 is not unpatentable over Andersson et al, Eljamal et al, Hanes et al, Radhakrishnan, and Swarbrick et al, either singly or in combination. As amended, claim 29 is to a method for the pulmonary administration of a dry powder composition comprising, *inter alia*: providing a dry powder composition comprising hollow and porous particles comprising: a phospholipid matrix, an active agent comprising tobramycin sulfate; a particle size of 0.5 to 20 microns; and a mass median aerodynamic diameter of less than 5 microns. The method further comprises: loading the dry powder composition into a passive dry powder inhaler having a range of flow rates; and administering the dry powder composition from the inhaler to the respiratory tract of a patient, wherein a fine particle fraction (FPF_{4+F}) emitted from the inhaler is at least 60% as determined by an Anderson Cascade Impaction or multi-stage liquid impinger, an emitted dose is at least about 60%, and is substantially independent of an inhalation flow rate, and wherein a lung deposition is greater than 25%, an interpatient variation in lung deposition is less than about 17%, and an intrapatient variation in lung deposition is less than about 6%.

For the same reasons cited above in the rejection of claims 1, 3-5, 11-15 and 21-34, neither Andersson, nor any of the other cited references discloses the features of claim 29, thus the claim is patentable thereover. Nor do the other references make up for the deficiencies of Andersson et al. Andersson et al does not disclose a pulmonary administration using a passive dry powder inhaler wherein the fine particle fraction is at least 60%. Eljamal et al, Hanes et al, Radhakrishnan and Swarbrick et al are not relied on to make up for this deficiency in Andersson et al, nor do they. Accordingly, no reference or combination of references arrives at an administration as recited in claim 29. Accordingly, the Examiner has not established a prima facie case under 35 U.S.C. §103(a).

For at least these reasons, claim 29 is not properly rejectable under 35 U.S.C. §103(a) as being unpatentable over Andersson et al, Eljamal et al, Hanes et al, Radhakrishnan and Swarbrick et al. The modification that would be necessary is not one that would have been well within the grasp of one of ordinary skill in the art at the time the invention was made. There is no evidence to suggest that this is a situation where the ordinary artisan could have been

motivated to modify Andersson et al in a manner that would result in the invention of claim 1, and there is no evidence to suggest the artisan would have seen the benefit in doing so. Thus, claim 29 is allowable over the references cited, and Applicants request the withdrawal of the rejection of claim 29 under 35 U.S.C. §103(a).

With further regard to the dependent claims, as the independent claims are allowable over the prior art of record, then their dependent claims are allowable as a matter of law, because these dependent claims contain all features/elements/steps of their respective independent claim. *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988). Additionally and notwithstanding the foregoing reasons for the allowability of amended independent claims 1 and 29, the dependent claims recite further features/steps and/or combinations of features/steps (as is apparent by examination of the claims themselves) that are patentably distinct from the prior art of record. Hence, there are other reasons why these dependent claims are allowable.

Claim rejections under judicially created doctrine of Double Patenting

The Examiner maintained the provisional rejection of claims 1, 3-5, 11-15 and 21-34 under the judicially created doctrine of double patenting as being unpatentable over the claims of U.S. Patent Applications Nos. 10/141,219 and 11/187,757 in view of Andersson et al and Hanes et al.

The Examiner further maintained the rejection of claims 1, 3-5, 11-15 and 21-34 under the judicially created doctrine of double patenting as being unpatentable over the claims of U.S. Patent No. 7,306,787 in view of Andersson et al.

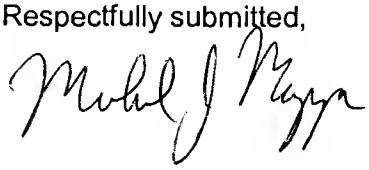
The double patenting rejections will be taken up and the appropriateness of filing a terminal disclaimer will be determined upon the indication of otherwise allowable claims.

Conclusion

The claims are allowable for the reasons given above. Thus, the Examiner is respectfully requested to reconsider the present rejections and allow the presently pending claims. Should the Examiner have any questions, the Examiner is requested to call the undersigned at the number given below.

The Commissioner is hereby authorized to charge any fees in connection with this Request to Deposit Account No. 19-0134.

Respectfully submitted,



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